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Review

Perisylvian epileptic network revisited

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We dedicate this paper to CA Tassinari, our spiritual master, who devoted so much work to exploring the nature of the strong link between NREM sleep and electrical status epilepticus in sleep (ESES).

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Rolandic epilepsy
Panayiotopoulos syndrome
Electrical Status epilepticus in sleep
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Cognitive impairment
Childhood developmental epilepsies

ABSTRACT

We overview here the new data about the epileptic spectrum disorders within the frame of perisylvian epileptic network since our first trial to synthetize knowledge about this system epilepsy (Halász et al., 2005). We found evidences for a continual features relating together syndromes constituting this spectrum disorder in several fields: in sharing genetic origin, in common perisylvian human communication circuitry, in NREM sleep related potentiation of interictal epileptiform discharges of the centro-temporal spike phenomenon and in the discharge related cognitive impairment, reflecting functional deficits in human communication abilities. The transformation of a part of the children to develop into a malignant course with different degree of residual cognitive loss, through compromising sleep plastic functions, by the epileptic discharges during sleep, beside pure genetic origin, is still under research. Both factual data and new conceptual approaches helps understand better the developmental childhood epilepsies.

1. Introduction

Thirteen years ago, we provided evidence for a unifying concept of idiopathic focal childhood epilepsies (IFCE): Rolandic epilepsy (RE), Panayiotopuolos syndrome (PS), Gastaut type childhood idiopathic occipital epilepsy,* Landau - Kleffner syndrome (LKS) and Electrical Status Epilepticus in Sleep (ESES) **. We treated them as a spectrum of disorders featured by a shared transient, age-dependent, genetically based, non-lesional and localized epileptic abnormality. The nature of this spectrum disorder is still not entirely clear. The electro-clinical features of the spectrum make a continuum of variable severity and localization conditions within the frame of the perisylvian cognitive network (human communication) [1].

* Gastaut type occipital epilepsy [2] is the smallest group (2–7%) of IFCE. Its interictal discharges (IEDs) and ictal symptoms unanimously delineate an occipital localization. It is an epilepsy of later childhood (the age at onset ranges from 3 to 15 years with a peak from 8 to 11 years) compared to RE and PS. The interictal signs are less variable and less fluctuating than in RE and PS. There is some overlap in the IEDs and age dependency with RE and PS, but the transformation to electrical status epilepticus in sleep (ESES/LKS) is less documented. Therefore, Gastaut type idiopathic occipital childhood epilepsy seems not to be part of the PN spectrum, and we will not incorporate it into this overview.

**Electrical status epilepticus in sleep (ESES) is the result of the malignant, atypical evolution of IFCE characterized by regional or global continuous IEDs during NREM sleep regardless of aetiology. It may cause severe cognitive loss, even without seizures and a structural lesion. LKS is the term for the syndrome of acquired childhood epileptic aphasia due to ESES-like regional or more diffuse IEDs during sleep regardless of the presence or absence of seizures.

There is a terminological lack of clarity concerning malignant encephalopathic forms of IFCE, especially in the use of the terms ESES and continuous spike-waves in sleep (CSWS) and the relation between LKS and ESES [3]. A source of contradictions is the interpretation of the electrical patterns of ESES. ESES is considered a synchronous bilateral

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spike-wave pattern by several authors, but abundant data support the uni-hemispheric, focal/regional localization of discharges [4]. The newly described variants increase the terminological and taxonomic confusion (see in Appendix A).

The members of the IFCE spectrum are age-dependent conditions, evolving in a time-window important for the development of human communication-specific skills.

In the past 13 years, our knowledge has increased. The spectrum view and the concept of epileptic networks have come to the fore. A most interesting and challenging approach tries to consider major epilepsies in the frame of physiological brain systems (system epilepsies) compromised in the early periods of brain development by an epileptic derailment of plastic processes in developmental epilepsies [5–9].

The prevalence of IFCE is approximately 15–20% in children younger than 15 [10,11]. Panayiotopoulos et al. [12] summarized the established and newly recognized syndromes of benign childhood focal epilepsies. Based on 30 years of clinical observations and research, they wrote: "All these conditions (established core syndromes of idiopathic focal childhood epilepsies (RE, PS and Gastaut type occipital epilepsy) and the newly described variants may be linked together in a broad, age-related and age-limited, benign childhood seizure susceptibility syndrome, which may be genetically determined" [13]. This elegant, grandiose paper did not deal with the increasingly evident transformation of the IFCEs to LKS and ESES, changing the benign outcome of affected children to a devastating encephalopathic form leaving 50% of them with permanent cognitive deficits.

Our paper [1] was the first to try to unify the benign, transient, age-dependent forms (IFCE) with the malignant encephalopathic variants (LKS/ESES), treating them as epileptic spectrum diseases of the perisylvian neuronal network (PN).

Since then, several groups of epileptologists contributed to the exploration of this syndrome-complex, raising almost all key questions of epileptology. In 2016, an important symposium was organized with the participation of clinicians and researchers working on the "lost tribe" of IFCE [14]. Lee et al. [15] expressed very similar views to ours in their synthetic work about the clinical spectrum of idiopathic childhood epilepsies with CTS.

As a further development of this story, it has turned out that ESES occurs in brain damaged children with variable aetiologies as well [16–19]. Several publications reported early thalamic lesions [20–24, 3], but few were shown to be isolated [21,4] [25]. It is unclear how different aetiologies can cause the same abnormality. There are studies exploring the complicated developmental anatomic relations of the perisylvian fissure [26], raising the possibility that shared genetic abnormalities may lead to variable cortical developmental changes from transient and macro-morphologically silent to gross and permanent dysplastic lesions. Perisylvian dysgenetic neuropathological lesions are nearly always polymicrogyria and may be related to abnormal flexure of the telencephalon in the late embryonic and early foetal periods.

Fejerman [27] delineated a group of patients who deviated from the classic course of RE with the possibility to evolve into a malignant epileptic encephalopathy in the form of ESES or LKS. He named this group atypical Rolandic epilepsy.

On the following pages, we discuss clinical experiences and research lines accumulated hitherto on different aspects of the perisylvian epileptic network.

2. The PN and regional distribution of communication functions

The PN harbours important human-specific cognitive functions. The frontal operculum, the first temporal convolution and the angular region around the end of the Sylvian fissure are regions mainly associated with speech and reading and other essential communication functions (Fig. 1). These perisylvian areas are strongly interlinked, forming a broader network called associative cortical areas, which also have rich connections with thalamic structures [28,29]. These connections are why some thalamic lesions may cause language disorders. Due to the spread of functional neuroimaging methods, the understanding of PN field involvement in speech functions and the interrelationship of RE with motor and language networks have quickly developed [30–33].

PN involves the arcuate pathway connecting Broca's and Wernicke's areas directly in the left hemisphere and an indirect pathway passing through the inferior parietal cortex running parallel and lateral to the arcuate fasciculus. This indirect pathway is made of an anterior segment connecting Broca's territory with the inferior parietal lobe and a posterior segment connecting the inferior parietal lobe to Wernicke's territory [34]. The bilateral PNs serve different cognitive functions: a representation of language and praxis in the left hemisphere and a representation of processes involved in spatial orienting in the right [35].

The degree of lateralization of perisylvian pathways is heterogeneous in the normal population, and paradoxically, bilateral representation might ultimately be advantageous for specific cognitive functions. Bilateral and symmetrical language representation is seen in 17.5% of normal humans and more likely in females [36].

3. Distinctive features of core IFCE syndromes and their interrelations

3.1. Topographic aspects

The PN hosting the disorder is localized around the Sylvian fissure strongly involved with communication and cognition. In RE, children have been reported to have some deficits in PN functions, such as writing, verbal expression, language comprehension and working memory [37,38].

RE mapping studies have shown that the axis of the characteristic dipole of IEDs overlaps with the Sylvian fissure [39]. The ictal symptoms suggest an anterior intra-Sylvian localization [40]. In RE, the most frequent seizure semiology is made by facial sensory, oropharyngolaryngeal motor symptoms, speech arrest, and salivation, suggesting a more or less congruent functional network suggesting the ictal involvement of the anterior part of the PN. A MEG localization study [41] showed that the cortical generators of Rolandic discharges (centrotemporal spikes; CTS) of RE are situated in the precentral motor cortex, which is closer to the secondary than the primary sensory cortex. There is, however, important variability in the shifting localization of CTS, especially in PS. Seizure symptoms in PS suggest central autonomic network involvement producing pallor, urinary or faecal incontinence, salivation, cyanosis, mydriasis or miosis, coughing, abnormal bowel movements, respiratory changes, irregular heartbeats and syncopal events [42]. These symptoms point to the insular and medial prefrontal cortex, amygdala and hypothalamus. Vomiting (also of insular origin?) is most frequent. A lower threshold of the immature autonomic system might underlie such symptoms [43].

The expectation of occipital semiology raised in PS by the overwhelming occipital CTSs seems not to be fulfilled. Occipital semiology is rare in seizures. The consensus view on PS [44] stated that PS should be classified as an autonomic, rather than occipital, epilepsy.

In LKS, the evolving aphasia refers to dysfunction in speech-related perisylvian opercular structures and/or the posterior part of the first temporal convolution. Some good results of the Morrell-type surgical intervention performed in these structures support this assumption [45]. In LKS, there is an important circumscribed continuous deficit of the speech network (mainly the posterior part) that is just mildly affected in the rest of IFCE.

Both LKS and ESES affect the PN, usually showing bilateral EEG changes. The dominant PN's involvement may cause speech loss in LKS and the widespread involvement of large cortical areas might be responsible for ESES's typical mental and behavioural deterioration. This widespread cortical involvement might be performed through the cortico-thalamic system [46].

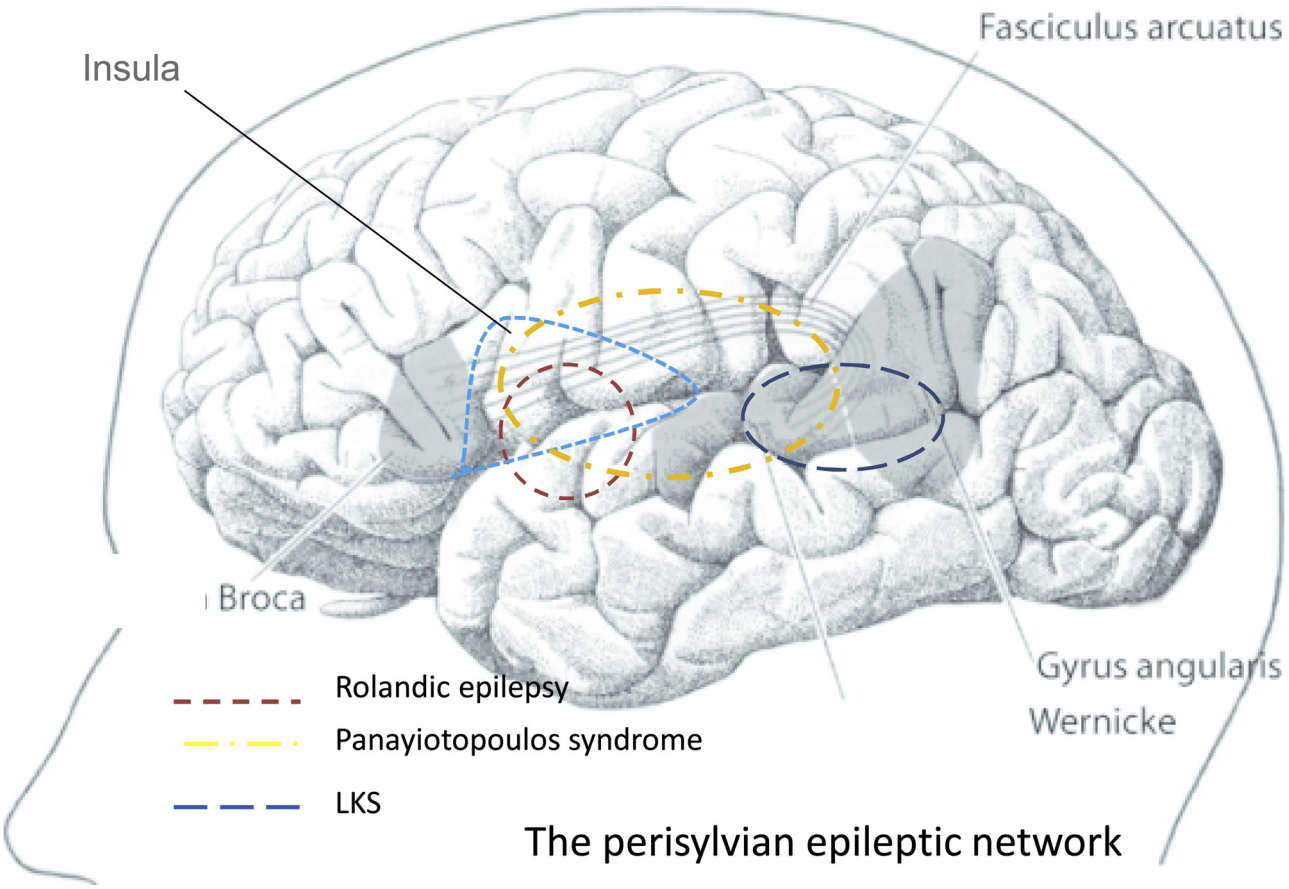

Fig. 1. The perisylvian epileptic network represented by spectrum of different syndroms. Their shematic distribution along the perisylvian fissure.

3.2. The interrelations of spectrum conditions

Although the constituting syndromes have clear distinctive characteristics of their own, they have overlapping and continual features, such as shared genetics, the CTS endophenotype and the essential influence of sleep on IED rate that determines the degree of cognitive impairment (see Fig. 2). The overlap and conversion of certain symptoms and features of RE in PS patients and vice versa occurs in some periods and patients creates another link [47]. The potential of IFCE to progress to LKS/ESES is an additional major feature unifying these conditions into one spectrum. It is unclear whether the activation of IEDs resulting in cognitive impairment in ESES/LKS is predetermined by genetic factors or it is due to a progressive evolution of epilepsy itself with possible contributions from additional environmental factors.

Concerning this malignant encephalopathic transformation, we have no relevant data about its prevalence. In the study by Tovia et al. [48], transformation was found in approximately 6% of IFCE children. Panayiotopoulos et al. [12], in their synthetic work, devoted only a small page to malignisation and treating it as a rare complication of IFCE occurring in cca. 1% of cases. Looking into the increasing focus on these conditions in the literature [4,14,48–60] and the estimations of involved professionals, it is likely that ESES/LKS is much more prevalent with an even higher heuristic significance.

3.3. Overlapping age dependency of PN epileptic syndromes

In each IFCE, the electro-clinical syndrome is associated with certain age groups in childhood and puberty. The symptoms of RE usually begin between 3 and 10 years and fade away by 15–16 years. In the reported cases, LKS had its onset from 4 to 7 years. The EEG abnormalities tend to subside with advancing age and disappear by age 15 in most cases. The beginning of ESES is typically 4–7 years with the EEG changes disappearing around puberty. The seizures, if there are any at all, show a benign course, but the variable degree of cognitive impairment is irreversible in half of encephalopathy cases.

3.4. Genetic aspects

The lack of lesional background in half of IFCE cases generated an early interest to genetic studies. After a long time without any breakthrough, recent findings have revealed several anomalies: the involvement of SRPX2 and ELP4 genes with possible roles in cell motility, migration and adhesion [53], changes in the GRIN2A gene encoding the NMDA receptor NR2A subunit as a major genetic risk factor for IFCE [61], and increased copy number variations in the RE-ESES/LKS in the genomic architecture of several genes (encoding cell adhesion proteins) [62]. The newest genetic meta-analysis [63] suggests that genetic factors underlie (causing channelopathies) the development of ESES/LKS, albeit the association of IFCE with ESES/LKS was not investigated in this study.

The search for genetic markers in lesional cases warrants further studies. Only a few children affected by early brain damage show potentiation of IEDs during NREM sleep. It is possible that also these children have a genetic predisposition not yet studied.

3.5. Centrotemporal spike (CTS) as a common endophenotype across PN epilepsies

Endophenotypes are genetically based common modules of phenotypically different complex disorders like schizophrenia, autism, attention-deficit hyperactivity syndrome (ADHD) and, certain epilepsies (Fig. 2). CTS is a common axis of PN conditions shared by autism

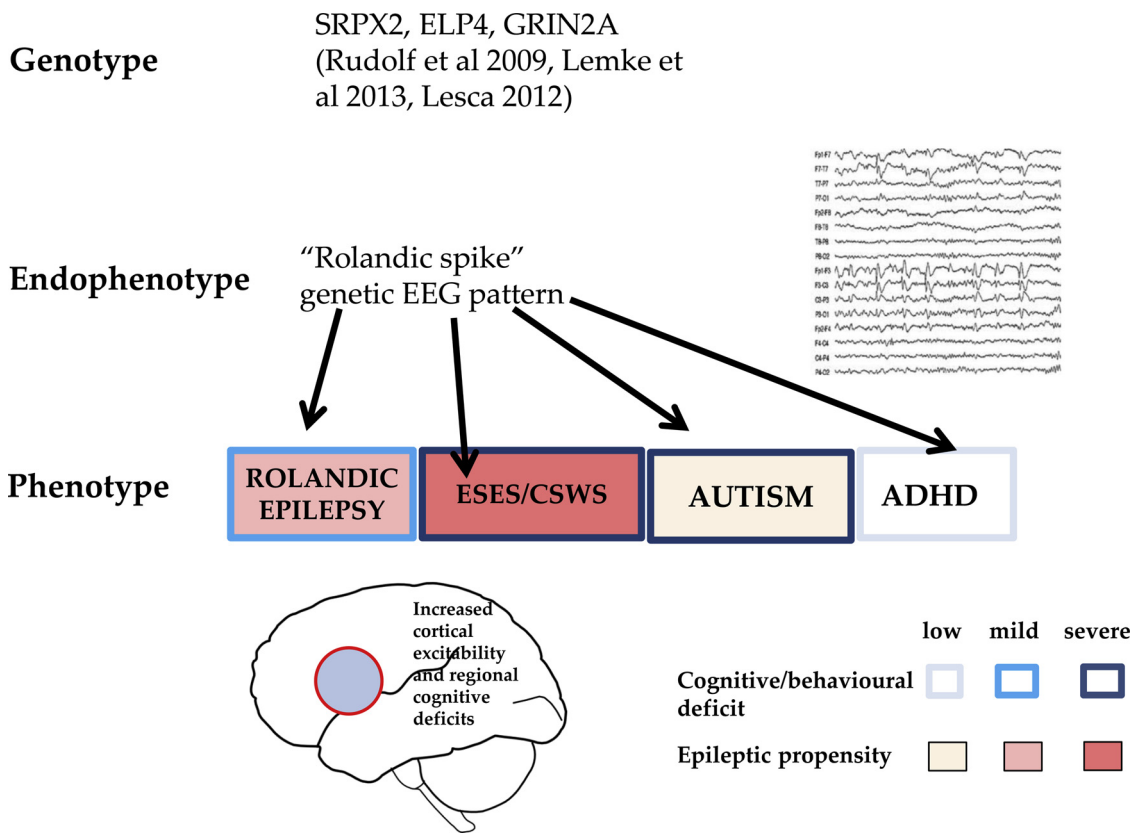

Fig. 2. CTS as a shared endophenotype in different disorders (Rolandic epilepsy, Electrical Status Epilepticus in Sleep, ADHD, Autism spectrum). Schematic representation of epilepsy propensity (red) and cognitive/behavioral deficits (blue). The first row shows hitherto recognised gene abnormalities. The middle row shows the CTS EEG pattern of Rolandic epilepsy Bottom: The territory of the red circle represents the area of increased epileptic excitability and cognitive deficits. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spectrum disorders [64,65] and ADHD [66–68] as well.

Tittering upon the edge of non-epilepsy and epilepsy CTS has a vague nature. It emerges in 2–4% of normal children without epilepsy [69,70] and always activates during NREM sleep. It may behave as an augmented evoked potential responding to acoustic and tactile stimuli [71,72]. in infants. Based on several studies, in cases where RE and PS patients had sleep recordings prior to their progression to ESES, the CTSs were similar to those later seen in ESES [73,74], with only quantitative differences, evidencing the spectral togetherness of those conditions. In ESES, the sleep-related CTS field is the same as during wakefulness [4] (Fig. 3). The degree of CTS potentiation during NREM sleep has been found to be similar with and without epilepsy [75].

Recently, Mirandola et al. [76] published a case report on a 13-year-old boy with moderate learning difficulties affecting reading, writing and calculation. He had no clinical epilepsy but did have right dominant bilateral independent CTSs importantly enhanced during NREM sleep that did not reach the 85% cut-off for ESES. Functional MRI (fMRI) in wakefulness revealed a right-sided increment of the BOLD signal in the bilateral sensory-motor cortex and a widespread CTS-related cortical-subcortical network over the PN and the connected thalamic region during NREM sleep. This case highlights that CTS during NREM sleep may link to a large pathological network, even without epilepsy.

CTS has an affinity to spindles [77–81] (Fig. 4) and, unlike the spikes of other epilepsies [77], is linked to the slow waves of the cyclic alternating pattern (CAP) A1 [82]. At the same time, since spindles are well known to couple with the upstate sleep slow waves, a link with slow waves seems plausible.

CTS is present as an IED in each member of the PN spectrum. In cases without seizures, no ripples are associated with CTS (Fig. 5 a, b). Ripples join them just in patients (RE) with clinical seizures. Even more ripples couple with the malignant encephalopathy course indicating the severity of epilepsy [83,84] (Fig. 5c). In addition to quantitative differences, the amplitude and frequency of ripples also differentiate the benign and malignant variants [85].

CTS is actually not a spike but a sharp wave with an 88 ms mean duration [39]. Its electro-morphology resembles the delta-brush of early premature infants [86,87] (Fig. 5d). Delta-brushes were shown to be important players in the development of the somato-topic arrangement of the sensory-motor cortex [86,87].

Based on the above data, we have to agree with earlier opinions of Doose and Baier [88] Panayiotopoulos [89], and Koutromanidis and Panayiotopoulos [13], suggesting that CTS might be the EEG sign of a local cortical developmental delay and increased local excitability with a potential to regress or progress to epilepsy, including its malignant variants.

3.6. Frequency and distribution of CTS during the waking state and NREM sleep

The prevalence rate of CTSs may vary from rare and random (1–3/10 s) to almost continuous. There is a large diversity in their topography—typically bilateral and independent or rare and bi-synchronous. CTSs may occur ipsi- or contralateral to the symptomatogenic side or multi-focally in RE. The most frequent combinations are bilateral and independent, posterior, centro-temporal, or occipital. Centro-temporal and occipital spikes frequently co-occur in PS, and some patients have more than two spike foci in one recording. Posterior variants show a shift towards more anterior fields over time [90,91] with shifting clinical features [92]. Typically, there is a leading hemisphere with secondary propagation to the contralateral hemisphere with a hemispheric dipole along the Sylvian fissure.

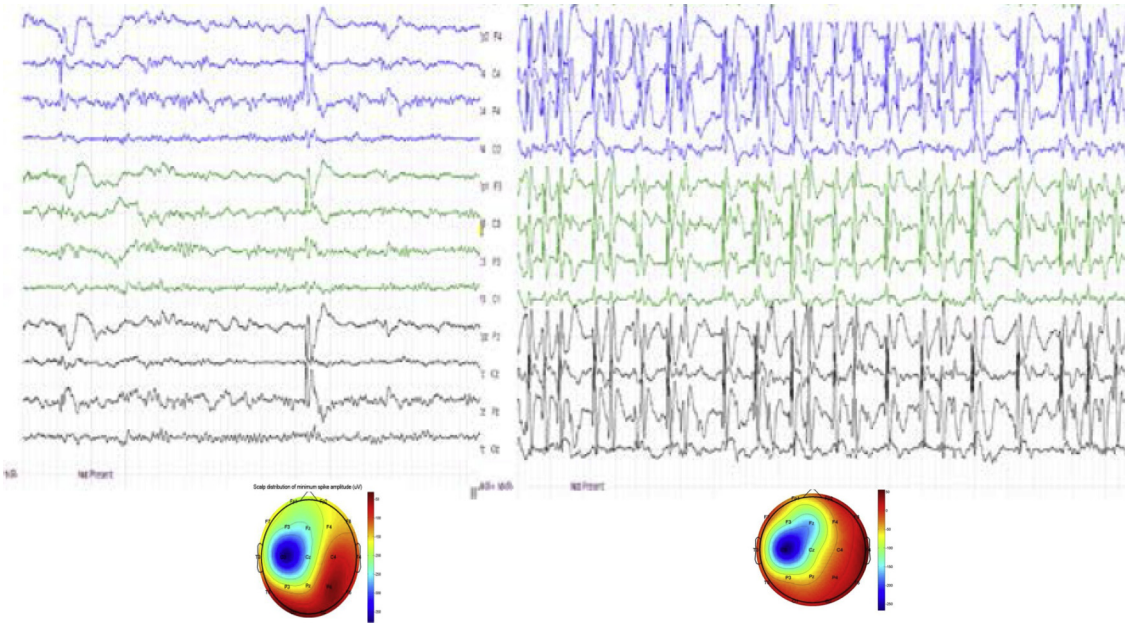

Fig. 3. Transition from wake state (left) to NREM sleep (right) shows the appearence of abundant spiking (ESES) during sleep in a 8 yrs boy. Below: amplitude mapping: averages of 10 awake (left) and 100 sleep (right) spikes. Note the similar pattern of the focal spike fields in awake and sleep condition.

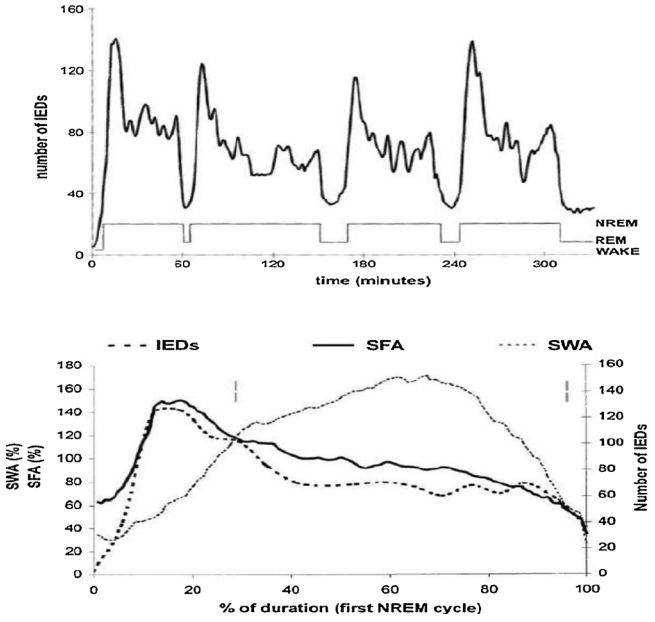

Fig. 4. The relationship between sleep oscillations and occurence rate of CTS among the spectrum perisylvian epileptic network disorders. Top: Distribution of CTS across the sleep cyclicity. Bottom: Distribution of IEDs (dashed line); the EEG sigma band (SFA = 12–16 Hz) and slow wave activity (SWA = 05–4.0 Hz) indicated by dotted line across the first NREM cycle. It is clearly seen that CTS goes parallel with sigma frequencies (sleep spindles), and not with SWA. (After Nobili et al., 2011).

One of the most interesting but unresolved issues is the shifting, unstable and multiple localization of CTS and the ictal symptoms mainly seen in PS (see also under the heading “topographic aspects”).

The frequent occurrence of IEDs around the big cortical sulci raise the possibility that the sophisticated gyral development of the cortex is associated with high vulnerability for maturational micro-defects.

These experiences tend to change the concept of PN epilepsies to more widespread, genetically based conditions of increased cortical excitability with shifting predominance. Instead of a small circumscribed area, the epileptic dysfunction is embedded in a broad network of associative cortices. The cortico-thalamic system seems to be a logical candidate for a relay station of excitability changes, which is similar to idiopathic generalized epilepsies (IGEs).

There are additional features connecting IGEs and PN epilepsies. Thirteen to forty percent of IFCE patients exhibit bilateral spike-wave discharges (SWDs) modulated by sleep and arousal, which is similar to the SWDs of absence epilepsy [93–95]. Degen and Degen [96] found SWDs even more frequently, in 65.1% of 43 children with RE and in 31.9% of their siblings. The possibility of a common genetic background of CTS/IFCE and SWD/IGE has been raised by several authors [97–99].

3.7. Rare seizures and abundant CTS-type IEDs

An additional shared feature of PN epilepsies is the rareness of seizures compared to other epilepsies. A possible explanation is the presence of closing slow waves in CTS, not allowing a longer depolarisation of cortical neurons necessary for the development of a seizure [1]. This feature, again, may put further question marks around the “true” epileptic nature of CTS.

3.8. NREM sleep involvement in the development of PN epilepsies

CTSs are frequent during sleep in RE patients. Clemens and Majoros [100] found that most of them occur in the first NREM sleep cycle and on the descending slope. In deep slow wave sleep (N3), the average spike number was 22/min versus 16/min in stage 1–2. There was a significant difference between the spike-count of descending and ascending slopes of the cycles with higher spikes on the descending slopes suggesting the role of homeostatic regulation. A further support for the effect of homeostatic regulation was the finding that the enhancement of CTSs correlated with delta waves and declined in line with the dampening course of delta from cycle to cycle.

Sleep studies evidenced strong spike potentiation during NREM sleep in IFCE, which was extremely enhanced in ESES/LKS. The earlier established rigorous diagnostic criterion for ESES, which was 85% coverage of NREM sleep by IEDs, has become more flexible recently (Sanchez et al., 2016). An important continuous regional, hemispheric or global activation of IEDs has been increasingly accepted for diagnosis

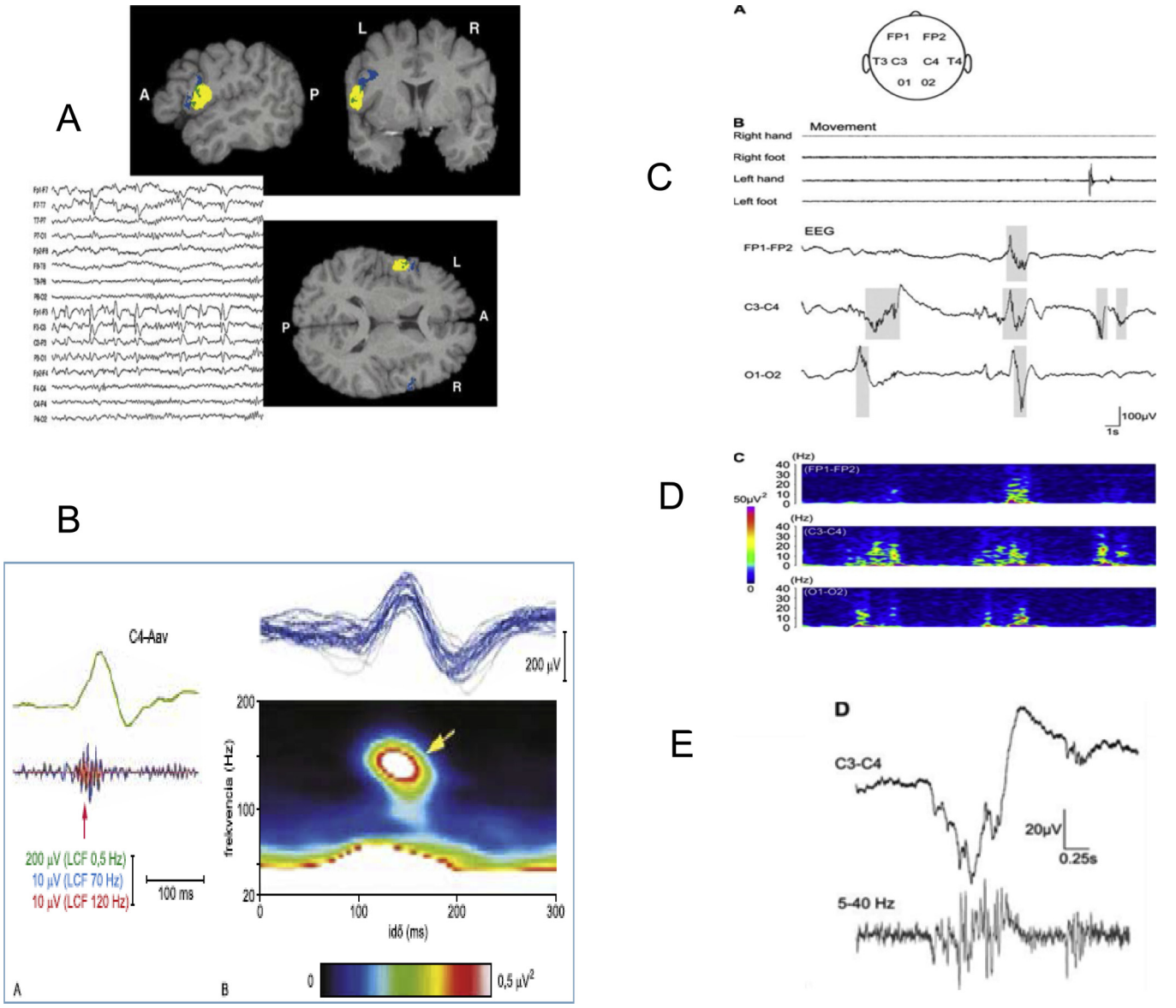

Fig. 5. Comparison of the centro-temporal spike (CTS) and the delta brush phenomenon. (**A**) Shows the characteristic EEG morphology and localisation by fMRI (after Manganotti et al., 1998). (B) Centro- temporal spike crowned by a ripple with around 120 Hz. (After [85]) (**C**) Spontaneous hand movements trigger C3–C4 delta-brushes in human 30 weeks postconceptual age neonate somatosensory cortex (after [87]). Upper trace: hand movement, middle trace: EEG response in C3–C4 filtered at 5–40 Hz. (D) wavelet –analysis. (E) delta-brush response with high frequencies nested in slow wave, in an extended time scale.

of ESES [101]. The continual features of sleep activation in time and space can be traced during the evolution and revolution of ESES [4] (Fig. 6). Thus, the view of ESES as a unique entity has turned into a spectral range concept, and the continuity between the IFCE and ESES/LKS groups of PN syndromes becomes clear.

The critical sleep enhancement of CTS is a defining feature of the whole spectrum. There is a continuity in the amount, synchronization, and bi-lateralization of spikes from benign IFCE to the malignant encephalopathy variants (Fig. 7).

An important sleep activation feature differentiating PN epilepsies from the rest of sleep-related epilepsies is the association of CTS with sleep spindling. The reason for this dichotomy across epilepsies, the coupling of IEDs with spindles or slow waves, is unknown. Considering the high likelihood that PN is a human neo-formation, its epilepsies must be phylogenetically new products as well. They are associated with and change with human communication functions, which are strongly attached to sleep spindling rather than to slow oscillations.

3.9. The origin of cognitive impairment unrelated to seizures

Earlier, we deemed that the presence or absence of cognitive impairment differentiates IFCE and ESES/LKS. Contrasting the view of the benign cognitive outcome of RE and PS, several recent publications involving large numbers of children have revealed a wide range of associated cognitive and behavioural disturbances, including in long-term storage and retrieval [102] and deficits in language and academic performance [103]. The cognitive deficits found in RE and PS link them with their atypical variants progressing to ESES and LKS.

Spiking obstructs slow oscillations in sleep, depriving the sleeping brain's synapses from refreshment for the next day [104,105]. Tassinari hypothesized this process in his famous metaphor calling ESES Penelope syndrome [106].

In ESES, the degree of cognitive decline depends on the length of the period with pathological sleep containing abundant IEDs. Usually, there is no residual deficit if this discharging period is shorter than 13 months, and a cognitive loss typically develops if it exceeds 18 months

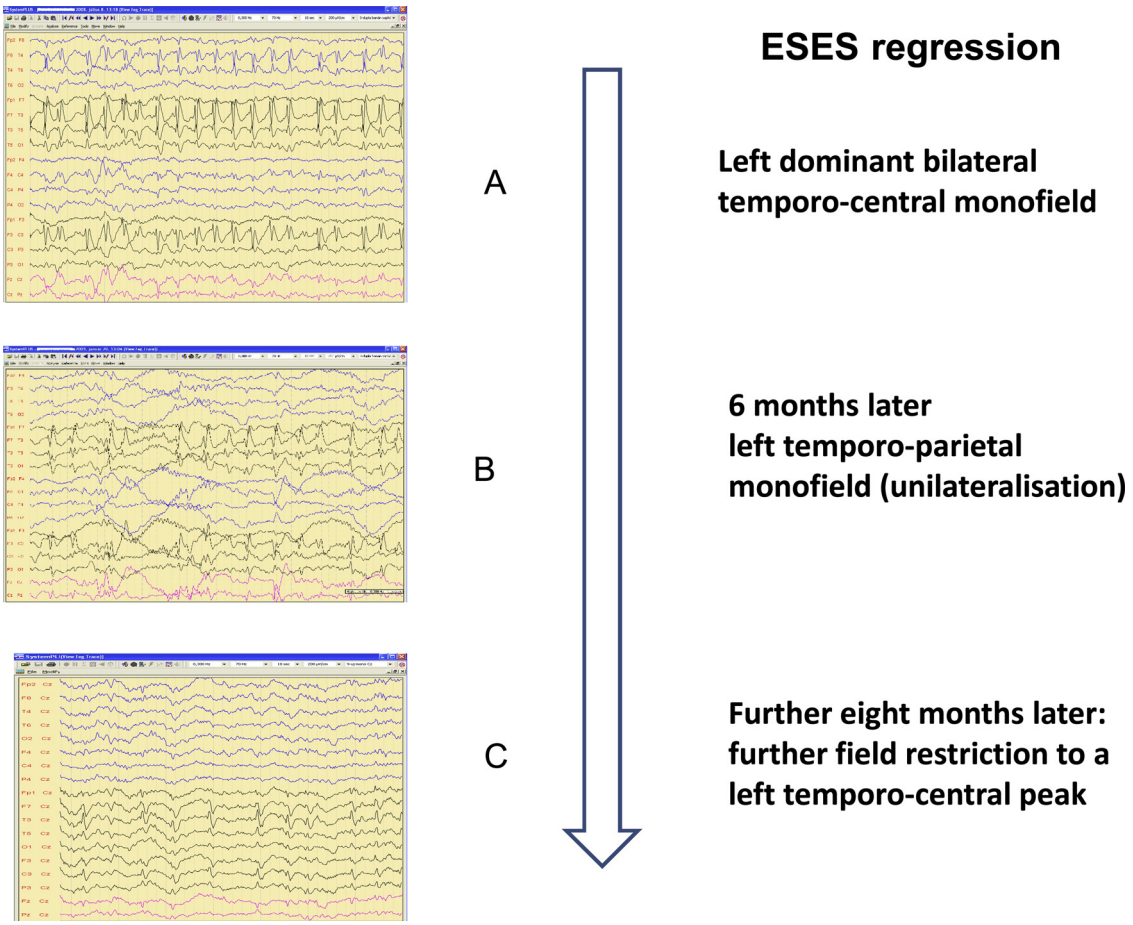

Fig. 6. Regression of spiking during remission of ESES. A: Left dominant bilateral temporo-central monofield, B: 6 months later left temporo-parietal monofield (unilateralisation), C: Further eight months later: more field restriction of the left temporo-central peak. perpendicular arrow represents the direction of regression process.

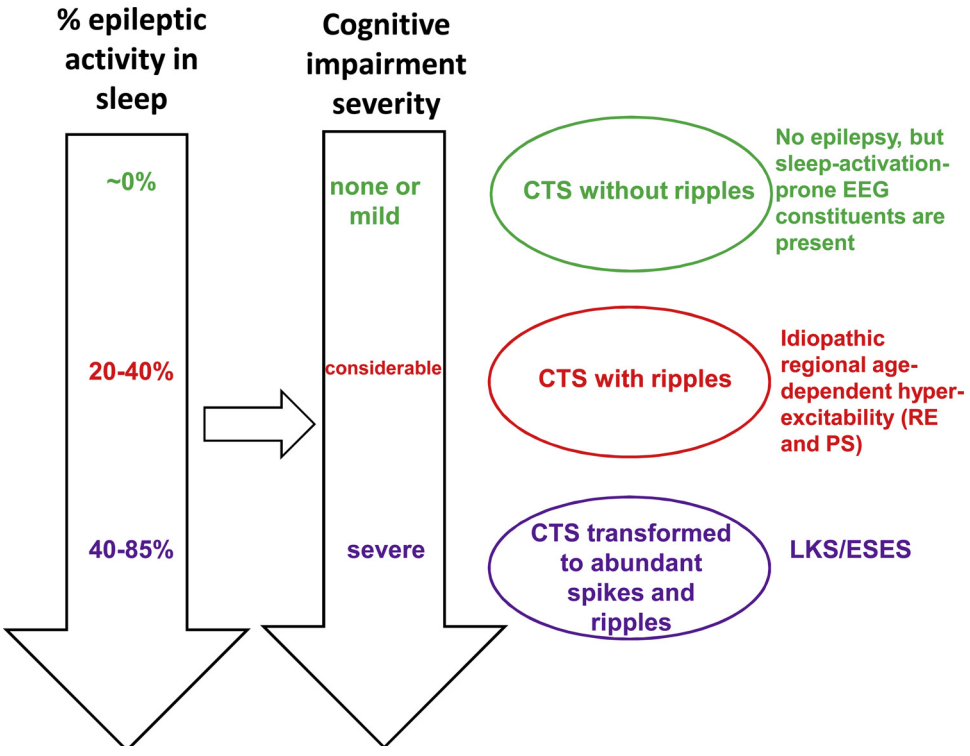

Fig. 7. Spectrum of syndroms witin the perisylvian epileptic network. Circles represents the the different conditions of the spectrum and their CTS containment Geen: without epilepsy; red: Rolandic epilepsy and Panayitopoulos syndrome; purple: Landau-Kleffner syndrome and Electrical Status Epilepticus in Sleep. The perpendicular arrows show continuum of the estimated sleep enhanchement of the interictal discharges left and the severity of cognitive impairment accross the spectrum. The horizontal arrow represents the assumed causative role of sleep discharges in cognitive impairment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[107,74]. At least 50% of patients remain severely impaired [108–110].

There is a strong correlation between the cortical localization of discharges and the disrupted function [106].

The amount of sleep-related IEDs and the degree of cognitive impairment seems to be correlated [106,4], suggesting that the cognitive decline is caused by the epileptic process. In addition to spikes, evidence has accumulated of the impact of pathological (epileptic) HFO in cognitive impairment [83–85], providing additional support for the causative role of IEDs.

Studies on the mechanisms of cognitive impairment recently explored two main pathways of IEDs interfering with sleep plastic functions. In LKS/ESES, spiking obstructs sleep's slow oscillations, depriving the sleeping brain's synapses from "refreshment" (upscaling) for the next day [104,105]. The other development of cognitive impairment is seen in human and experimental medial temporal lobe epilepsies where hippocampal IEDs interfere with encoding and consolidation of memory engrams leading to selective memory disturbances [111–115]. Naturally, these data require further support.

3.10. Shared circuitry

As was shown, the cortical circuit of PN epilepsies is large, involving the somato-sensory, autonomic and visual cortices. Typically, the posterior speech areas are involved in LKS, and in ESES, the bilateral cortical mantle may be diffusely affected. The dynamics of the stochastic process governing the seemingly random flashing discharges that fluctuate in time and space is unknown. It seems more consonant with the "epileptic hyper-excitability" concept of Panayiotopoulos [13] and Koutroumanidis and Panayiotopoulos [116], than the static notion of interictal spike foci in most epilepsies.

The cortico-thalamic system and default mode network involvement were shown by fMRI studies [46] in ESES/LKS. There is some experimental evidence supporting the possibility of activation limited to regional subsystems (sectors) of the cortico-thalamic system. This idea goes back to Gastaut, who tried to explain the similarities and differences in IFCE and IGEs by the sectorial involvement of the cortico-thalamic system. Basically, the cortico-thalamic association system is built by modules of regional reciprocal connections between thalamic and cortical structures. In epileptic ß3 mouse mutants, Huguenard [117] registered network responses in thalamic slices that resembled the activity of absence seizures, but this activity remained restricted to a sector of the slice. The theory of sectorial involvement of the cortico-thalamic system in RE helps to overbridge the differences between the partial and generalized features of CTS and SWD.

4. Discussion

PN epilepsies share several qualitative features, and they may be arranged in a quantitative continuity based on their severity, as shown in Fig. 7.

The PN epilepsy spectrum is extended by LKS/ESES malignant encephalopathy variants of IFCE in addition to the benign core conditions of RE and PS. ESES/LKS may represent a common pathway of evolution for IFCE, leaving half of affected patients with permanent cognitive impairment.

The inherent involvement of ESES/LKS in the PN epilepsy spectrum is supported by the following:

a) The morphologically same discharge pattern of CTS featuring in each condition from IFCE to ESES, making CTS an axis and an endophenotype of the whole spectrum.
b) The potentiation of IEDs by NREM sleep in ESES, similarly but more markedly than in RE.
c) The degree and regional distribution of spiking correlating with the degree and type of cognitive impairment in each involved condition.
d) The same age windows for IFCE and LKS/ESES.
e) A low seizure proneness and high interictal activity across the spectrum.
f) There are shared genetic features.

Despite the genetic background, a lesional aetiology is reported in almost half of ESES cases. At the same time, even in such cases, yet unexplored genetic factors might contribute to the malignant course.

NREM sleep potentiation of IEDs seems to be a marker of severity and outcome in each syndrome (phenotypes) of the spectrum. There is intensive work worldwide looking for better understanding of the close connection of NREM sleep and epilepsy. The way that IEDs interfere with sleep plastic functions compromising the "refreshment" of synapses during slow wave sleep has remained a major issue [104–106]. PN epilepsies are a model highlighting the pathophysiology of developmental epilepsies and revealing unknown pathways of cognitive impairment occurring without seizures or parenchymal brain damage. *

The newest constituents of PN epilepsies are the high frequency oscillations (HFO = ripples) on the top of the CTS. The absence, presence, prevalence and some qualitative features (e.g., amplitude) of ripples indicate the severity of the syndrome, especially the cognitive impairment.

Studies of PN epilepsies highlight the ineffectiveness of antiepileptic drugs that provide defence against seizures unlike the interictal epileptic process.

There remain several important issues still without explanation. Two of these issues seem to be the most urgent to solve:

The CTS phenomenon, which seems to be the key to understanding the relationship between developmental cortical immaturities, epileptic hyperexcitability and sleep plastic functions.

Whether PN spectrum conditions are genetic variants of genetically predetermined malignization or the malignant transformation is due to a per se epileptic self-strengthening evolution fuelled by IEDs.

*This issue seems to be parallel to lessons from child psychiatry in the understanding of psychopathology.

5. Conclusions

We summarized clinical experiences, new research lines and results for epileptic spectrum disorders of the perisylvian network since our first trial to synthetize knowledge about these system epilepsies [1]. Enriched by new data, we see that PN anchors the spectrum of idiopathic, age-dependent, regional, interrelated syndromes. They share genetic origins. They have a CTS endophenotype as an axis across the involved syndromes and seizure semiologies reflecting the represented communication-related functions. Abundant interictal discharges and low seizure proneness feature in each member of the spectrum, and there is cognitive impairment of variable severity proportional to the degree of sleep-related interictal discharges.

PN conditions represent system epilepsies of the human communication network and provide examples of cognitive impairment without seizures and brain damage by IEDs that interfere with sleep plastic functions. They help us better understand the nature of early childhood developmental epilepsies.

Conflict of interest

The authors have no conflict of interest.

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Appendix A. Recognized variants of IFCE

1) Age-dependent childhood epilepsy with short affective (screaming,

terror) and autonomic ictal symptoms in waking or sleep and interictal fronto- or parieto-temporal stereotypical spikes [122,123]. There is remission within 1–2 years and good treatment response. Behavioural issues may occur during the active phase. The clinical phenotype resembles RE and PS.

2) Idiopathic childhood epilepsy with spikes elicited by tactile stimuli and somato-sensory extreme evoked potentials [124,72] with RE or PS. Versive seizures with impairment of consciousness occur. There is an excellent response to treatment, and the condition fades away within 1–2 years, but EEG signs persist longer.
3) Idiopathic childhood focal seizures and frontal [125–127] or midline [127,128] spikes. The topographic significance of the spikes is unclear [12]. Bureau et al [129] and Capovilla et al. [128] described a syndrome called idiopathic infantile focal epilepsy with midline spikes during sleep characterized by brief seizures with arrest, cyanosis, and impairment of consciousness and stiffening of the arms. The seizures start within the first three years of life and cease by age 4. There are small midline spikes during NREM sleep.
4) An atonic variant of IFCE with CTS [130] was found in 7 (5%) out of 48 IFCE children. Its features are early (mean 2.4 years) onset, axial or axorhizomelic atonic seizures several times per day or week that are worsened by carbamazepine. Immunotherapy was successful.
5) Several patients presented with ictal like palsy of the lips, tongue and throat with drooling and slurred speech, swallowing difficulties, and occasional weakness of the face with typical CTS from 3 to 5 years of age. The ictal periods were longer, and the recovery was slower compared to classic RE patients. In a published case, the ictal symptoms were underscored by continuous spiking over the motor opercular region [131–134].
6) Atypical benign focal epilepsy of childhood with pseudo-Lennox syndrome features. [51,135]. In addition to classical seizures of RE and PS, various other types of seizures may also occur (secondary generalized tonic-clonic seizures, atypical absences, myoclonic and atonic seizures). Cognitive impairment and behavioural and speech symptoms may occur. Waking EEG may show CTSs and sleep EEG resembles ESES. The seizures show poor responsivity to pharmacotherapy. Seizures tend to disappear before adolescence, but there remains neuropsychological deficits.

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